NEUROPATHIC PAIN, CLINICAL AND MANAGEMENT ASPECTS

R.D. Chirileanu, M. Simu, D. Reisz, C. Rosca, S. Males, R. Tocai
Neurology Clinic, Timisoara, Romania

The International Association for the Study of Pain (IASP) defines the neuropathic pain as "pain resulting from disease or damage of the peripheral or central nervous system, and from dysfunction of the nervous system". Pain can occur after injuries at any level of the nervous system: peripheral, central or autonomic. The sympathetic nervous system may be also affected, causing sympathetically maintained pain.

ETIOLOGY OF NEUROPATHIC PAIN

The neuropathic pain is a debilitating condition characterized by severe, relentless chronic nerve pain, caused by a primary lesion or dysfunction of the nervous system, and it is often a complication of common diseases including diabetes, herpes, stroke, multiple sclerosis, HIV infection, traumatic injury or surgery, alcoholism, cancer and its treatments. It is important to note that any type of a lesion (e.g., infectious, neoplastic or vascular) can produce pain if it affects the pathways of pain transmission.

Based on the anatomical site of the lesion, neuropathic pain may be classified in central neuropathic pain, peripheral neuropathic pain and mixed neuropathic pain (central and peripheral). There are many etiologic causes of neuropathic pain:

1. Causes of central neuropathic pain include injuries or dysfunctions of the:
- spinal root/dorsal root ganglion (prolapsed disc, arachnoiditis, post-herpetic neuralgia, trigeminal neuralgia/root avulsion, tumour, surgical rhizotomy)
- spinal cord (trauma including compression, syringomyelia and intrinsic tumours, multiple sclerosis, hemorrhage, AVM, spinal dysraphism, vitamin B 12 deficiency, HIV, syphilis, anterolateral cordotomy)
- brain stem (lateral medullary syndrome, multiple sclerosis, tumours, tuberculoma)
- thalamus (stroke, tumours, haemorrhage surgical lesions),
- sub-cortical and cortical brain (stroke, trauma, AVM, tumour)

2. Causes of peripheral neuropathic pain include:
- mononeuropathies and multiple mononeuropathies (trauma: compression, transection, post-thoracotomy, painful scars; diabetic mononeuropathy and amyotrophy, neuralgic amyotrophy, connective tissue disease, malignant and radiation plexopathy, trench foot, borreliosis)
- polyneuropathies:
  - metabolic/nutritional (diabetic, alcoholic, pellagra, Beri-Beri, burning feet syndrome, amyloiditis),
  - drugs (Cisplatin, Isoniazid, Vincristine, Nitrofurantoin, Disulfiram)
  - toxic (Arsenic, Thallium, Clioquinol),
  - infectious (HIV, acute inflammatory polyneuropathy (Guillain-Barre) / CIDP)
  - hereditary (Fabry's disease, dominantly inherited sensory neuropathy/ HSAN)
  - malignant (myeloma, carcinoma)
  - idiopathic small fibre neuropathy.

PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

Neuropathic pain is a pathological state at peripheric levels, within the dorsal horn and it affects also higher central structures. The main key points regarding the pathophysiology of the neuropathic pain are the following:
– The A? and C primary afferent neurons transmit the coded noxious stimuli to the dorsal horn of

Author for correspondence:
Denisa Pirscoveanu, Neurology Department, Neuropsychiatry Clinical Hospital, Medicine and Pharmacy University, 129 Calea Bucuresti, Craiova, Zip Code 200620, Romania
email: denisapirscoveanu@yahoo.com

the spinal cord.
- In the dorsal horn the neurotransmitters glutamate and substance P are responsible of the transmission of the noxious stimuli
- The damage of the peripheral nerves cause reduced firing thresholds, activation of adjacent normal nerves (cross-talk) and ectopic discharges
- The direct damage of the central nervous system or an abnormal peripheral input lead to hyperexcitability and inhibition loss
- The neuropathic pain has an impact on the descending inhibitory pathways from higher brain levels

The pathophysiology of neuropathic pain is complex, involving both peripheral and central mechanisms.

PERIPHERAL MECHANISMS

A peripheral nerve injury causes sensitization characterized by neuronal spontaneous activity, reduced thresholds for activation and increased responses to given stimuli. If the injured nerve is a nociceptor, then the increased nervous discharge will lead to increased pain. The C-fibre nociceptors can create sensitivity and new adrenergic receptors which explain the sympathetically maintained pain. Apart from that, ectopic neuronal pacemakers can be formed along the length of the injured nerve because of dysfunctional sodium channels. The sodium channels in injured nerves have other depolarization characteristics.

It has been shown that between adjacent demyelinated axons abnormal electrical connections, called ephapses, can occur. Damaged nerves contain ephapses between symphatetic and sensory fibres, so that these cross-connections play an important role in the pathogenesis of sympathetically mediated pain.

Neurogenic inflammation is a cause for hyperalgesia. The prostaglandins (PGE2) and substance P are released from primary afferent nociceptors and sympathetic postganglionic neurons, activating the nearby receptors and spreading activation.

Peripheral neuropathic pain can be caused by dysfunctions or damage of the peripheral nervous system including the cranial nerves (except the optic nerve), peripheral nerve trunks, dorsal root ganglia, spinal nerve roots, nerve terminals. The result is analgesia and loss of sensation in the damaged area, and the sensory, motor, autonomic or mixed nerves are affected, leading to paradoxal pain in the hypo-aestethic area.

There are various painless neuropathies due to the loss of pain sensation, such as: Tangier disease, leprosy.

The clinical examination of peripheral nerves show the presence of: allodynia, hypo- or hyperaestesia, hyperpathia, hypo- or hyperalgesia, parasesthesia, neurological deficit, vasomotor dysfunction, autonomic dysfunction, Tinel`s sign.

The causes of peripheral pain are: diabetic neuropathy, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, post-surgical neuropathic pain, post- traumatic neuropathic pain, nerve compression and entrapment neuropathies, HIV infection, cancer, complex regional pain syndrome, hereditary neuropathies, toxic neuropathies, deficiency states, hypothyroid neuropathies, Guillain-Barre syndrome, autoimmune neuropathies.

CENTRAL MECHANISMS

After a peripheral nerve injury, anatomical and neuro-chemical alterations can occur in the central nervous system (CNS). They can persist long after the injury has healed. This "CNS plasticity" plays a significant role in the evolution of chronic, neuropathic pain.

Sensitization of neurons can as well occur in the dorsal horn, the result being peripheral tissue damage. This is manifested through increased spontaneous activity of the dorsal horn neurons, a decreased threshold and cell death in the spinal dorsal horn. In a non-injured state, the A beta fibers (large myelinated afferents) penetrate the dorsal horn, travel ventrally, and end in lamina III. The C fibers (small unmyelinated afferents) penetrate directly and they end in lamina II. After a peripheral nerve damage there is a prominent sprouting of large afferents dorsally from lamina III into laminae I and II. After peripheral nerve injury, these large afferents gain access to the spinal regions which are responsible of the transmission of high intensities and noxious signals.

Some important alterations located in the dorsal horn ipsilateral to the injury have been discovered. Peripheral nerve injury may lead to increased mRNA for specific neurotransmitters (e.g., substance P), decreased levels of opiod binding sites, occurance of early gene products (e.g., c-fos). The conclusion is that peripheral nerve damage causes changes in the cell's synthesis of products,

and alterations in the production of neuropeptides/ neuromodulators.

The injured axon releases factors which initiate important changes for the development of pain. Thermal hyperalgesia has been prevented by blocking axonal transport bidirectionally with colchicines. Repetitive damaging stimulation of unmyelinated C-fibers cause prolonged discharges of dorsal horn cells, a process called "wind-up". Repetitive episodes of "wind-up" can lead to long-term potentiation (LTP), which involves a long lasting increase in the efficacy of synaptic transmission. Apparently "wind-up" is known to last a few minutes, but LTP generally lasts from one hour to even months. Both "wind-up" and LTP are believed to be part of the sensitization process involved in various chronic pain disorders.

Studies confirm the fact that excessive nociceptive input to the dorsal horn leads to excitotoxic consequences causing the death of inhibitory interneurons. This inhibition may contribute to spinal hyper-excitability.

CLINICAL FEATURES OF NEUROPATHIC PAIN

Neuropathies are characterized by burning, shooting, stabbing or electric pain. Paresthesias, which are expressed through numbness and a tingling sensation also occurs, along with allodynia (increased sensitivity and pain with normal touch). The pain often persists continuously, regardless of the patient's activities. In many cases, pain strikes in sudden attacks without any apparent trigger. The diagnosis is based on the patient's history and physical examination. Testing usually offers an insignificant clinical benefit unless the testing is looking for a treatable cause.

The lab tests should include the following:

1. A blood count (CBC) and sedimentation rate (ESR)
2. Thyroid testing with a Free T4 and TSH
3. Vitamin B12 level
4. Screening for diabetes with a morning fasting: blood sugar and a glycosylated hemoglobin (HgBA1C)

TREATMENT

- **Antidepressants and anti-epileptics**

Tricyclic antidepressants such as Amitriptyline and Imipramine inhibit the pre-synaptic uptake of Serotonin and Noradrenaline, interact with sodium and Calcium ion channels and block some post-synaptic Hystamin and muscarinic receptors. The usual starting dose of Amitriptyline is 25mg daily, titrated to a mean of around 75mg.

More selective antidepressants include Paroxetine and Fluoxetine (Serotonin inhibitors), Venlafaxine (inhibitors Noradrenaline and Serotonin), Duloxetine (diabetic neuropathy).

- **Anti-epileptic pharmacology**

Carbamazepine and Phenytoin block voltage dependent Sodium channels and Carbamazepine has additional actions via serotonergic pathways. Newer antiepileptics such as Gabapentin, Pregabalin and Lamotrigine have actions on receptors voltage dependent Calcium channels and modulations of GABA synthesis. The doses of antiepileptics used are similar with the ones used in epilepsy.

- **Local anaesthetics and other pharmacological approaches**

A Lidocaine patch is applied on the area where the pain is experienced. A small proportion of Lidocaine is contained in the patch (5%). The time to achieve an effect is measured in hours to a few days.

Capsaicin is a medicine that derived from the chilli pepper. Pain reduction is achieved by the capacity of Capsaicin to inhibit the release of substance P from nerve endings and to reduce the density of epidermal nerve fibres. The resultsoccur after at least 2 to 4 weeks. Capsaicin cream is commercially available in 0.025 and 0.075% concentrations.

Clonidine is available in a patch formula and it is used by transdermal administration.

Oral agents such as Mexiletine (50-150mg), Baclofen (10-20mg), Tizanadine (4-8mg), Cannabinoids, 5HT3antagonists (4mg), Cholecystokin antagonists have effects in neuropathic pain.

Parenteral agents are used when the oral administration is unavailable (severe vomiting, or it is insufficient when a rapid titration of drug is needed). The drugs used are Lidocaine (500-1000 mg), Phenytoin (600 mg), Posphenytoin (500-1000 mg), 5HT3 antagonists (Odanestrone = 8mg), Adenosine.

Ketamine has effects in peripheral neuropathic pain, central neuropathic pain, ischaemic pain, cancer. Ketamine is used in subanaesthetic doses. Oral dosis is usual 10-60mg, four times per day. There are reports of higher doses up to 100mg. In parenteral administration Ketamine is administred

by continuous subcutaneous infusion. The usual dose range is 50-600mg per day and it should be diluted with 0.9% saline.The contraindications in administrating Ketamine are: incontrolled hypertension, raised intracranial pressure, psychosis, epilepsy.

Other NMDA receptor antagonists are Magnesium and Dextromethorphan.

- **Opioids**

The evidence supports the use of Morphine, Oxycodone and Tramadol in neuropathic pain, and Methadone, Buprenorphine and Fentanyl may have good results, but they are supported by less evidence. There are three opiod receptors that mediate analgezia: kappa, μ and delta. Once activated, they inhibit Glutamate release and hence inhibit the transmission of nociceptive stimuli from C and A delta fibres, may also reduce gamma aminobutyric acid which is the inhibitory transmitter in the brain.

Morphine has effects in patients with post herpetic neuralgia, diabetic neuropathy, central neuropathic pain.

Oxycodone has a greater potency that morphine, 1mg oral oxycodone = 2 mg morphine. Oxycodone is available as tablets and solutions as well as injections. In combination with Paracetamol it is a very useful drug for cancer and non cancer pain.

Tramadol is considered a weak opioid , it is five to eight times less potent than Morphine. It is available as normal release and sustained release tablets. Tramadol has been evaluated in patients with post herpetic neuralgia and diabetic neuropathy.

- **Transcutaneous electrical nerve stimulation (TENS) and acupuncture**

TENS is the delivery of pulsed electrical currents across the intact surface of the skin in order to stimulate the underlying nerves. TENS is non-invasive, the effects are immediate, it is useful in trigeminal neuralgia, postoperative pain, post herpetic neuralgia, shoulder pain, low back pain, sciatica, diabetic neuropathy of feet, etc. TENS is contraindicated for patients with cardiac pacemaker or cardiac problems.

Accupuncture can be used when patients do not respond to TENS. It is contraindicated for patients with pacemaker, anticoagulant medication, pregnancy, spinal cord stimulation. Electrodes are placed in the epidermal space via percutaneous needles or in open surgery. The power source is usually implanted and it is similar to a cardiac pacemaker, it is effective for ischaemic and neuropathic pain.

REFERENCES:

1.Oxford pain management library. *Neuropathic pain.* 2007 edition

2.Medtronic pain therapies. Neurostimulation for the management of chronic neuropathic pain. 2005 edition

3.Marco Pappagallo – The neurological basis of pain. McGraw-Hill ed. 2005

4.Woolf CJ, Mannion RJ – Neuropathic pain: etiology, symptoms, mechanisms, and management. *Lancet* 1999; 353:1959

5.Bennet M – The LANSS Pain Scale: The Leeds assessment of neuropathic symptoms and signs. *Pain* 2002; 92:147.

6.Suzuki, R. and Dickenson, A.H. – Neuropathic pain:nerves bursting with excitement. (2000) *Neuroreport*, 11, R17-21.

7.Tracey, I. – Functional connectivity and pain: how effectively connected is your brain? (2005). *Pain*, 116, 173-4.

8.Bennet DS and Cameron TL – Spinal cord stimulation for complex regional pain syndromes. In Simpson BA (Ed), Electrical stimulation and the relief of pain, *Pain Res and Clin Man.* Vol 15 (pp111-129). Elsevier, Amsterdam 2003.

9.Fields HL – Painful dysfunction of the nervous system: pain. McGraw Hill, New York, NY, 1987

10.Backonya, M.M. – Defining neuropathic pain. (2003). *Anesth. Analg.*, 97, 785-90

11.Bennet, G.J. – Neuropathic pain: a crisis of definition? (2003). *Anesth. Analg.* 97, 619-20

12.Grond S, et al. *Pain.* 1999:79:15-20

13.Backonja M. – Pathogenesis and treatment of neuropathic pain in older adults. *American Journal of Pain Management.* April 2004;14(2):9S-185.

14.Sindrup SH, et al. – Tramadol relieves pain and allodynia in polyneuropathy: A randomized, double-blind, controlled trial. *Pain.* 1999;1:85-90.